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EVIDENCE FOR DIRECT STIMULATION OF THE MAMMALIAN NERVOUS SYSTEM WITH IONIZING RADIATION

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ABSTRACT

In a behavioral study designed to detect the most immediate reaction of the intact nervous system to ionizing radiation, rats were exposed while asleep to X rays (250 kvp), and measurements of behavioral arousal and heart rate were made to indicate activation of the central nervous system. A transitory behavioral arousal was exhibited within 12 seconds at an exposure rate of 0.25 r/second. At a higher dose rate of 1.9 r/second this initial reaction increased in scope and by 30 seconds included sub-cortical activation as well, as indicated by a heart rate response. These reactions depended upon the rate of exposure and not upon the total dose. In blinded animals, exposure at the high intensity evoked both the behavioral arousal and the heart rate response. This indicates that CNS activation cannot be attributed to the direct effect of radiation on the visual receptor system. Although radiation may act as a stimulus to the CNS through other sensory systems it was also suggested that the nervous system itself is directly sensitive to ionizing radiation.

NON-TECHNICAL SUMMARY

The Problem

This study was undertaken to provide evidence of an immediate reaction of the intact mammalian nervous system to low intensity exposure to ionizing radiation.

The Findings

X-ray exposure acts as a stimulus to the nervous system in the rat as evidenced by its power to produce behavioral arousal in the sleeping animal within 12 seconds at an exposure rate of as little as 0.25 r/second. At a higher dose rate of 1.9 r/second this initial reaction is subsequently increased in scope and includes subcortical activation as indicated by the presence of a change in heart rate by 30 seconds. These reactions depend upon the rate of exposure and not upon the total dose. Since the response is present in blinded as well as normal animals it cannot be attributed to the direct effect of radiation on the visual receptor system. The most probable basis for the effect is that the nervous system is directly sensitive to ionizing radiation.

EVIDENCE FOR DIRECT STIMULATION OF THE MAMMALIAN NERVOUS SYSTEM WITH IONIZING RADIATION

Investigations dependent upon neurophysiological and histological techniques have generally failed to produce evidence of any marked reactivity of the adult mammalian nervous system to ionizing radiation (1). Behavioral methods have been used to demonstrate that a low dose level of radiation can act as an unconditioned stimulus in the conditioning of avoidance responses (2), and it was considered likely that a behavioral criterion might also be utilized to detect the most immediate effects of radiation stimulation in the intact mammalian nervous system.

For this purpose, rats were exposed to X rays while asleep in a glass exposure chamber (Fig. 1.) and observational measurements of behavioral arousal were made. Heart rate measurements were also made to provide additional evidence of central activation during the arousal response (3,4,5).

Young adult, male, Sprague-Dawley rats served as subjects. Prior

Fig. 1 Cut-away version of observation-exposure chamber with rat in a sleep position and connected for recording of EKG.

to radiation exposure the animals received 40 hours of adaptation (6) which included exposure to X-ray machine and room noises. Heart rate values during the sleep state, obtained in the last 8-hour period of adaptation, were used to equate experimental groups.

Behavioral arousal was measured by means of a rating scale which provided identification of <u>any</u> visible departures from the condition of sleep or complete inactivity. The viewing distance through a leaded-glass window to the X-ray room ranged from 2 to 5 meters. Three trained observers typically showed better than 90% agreement on independent ratings made in a series of reliability tests. Heart potentials were recorded on a four-channel oscillograph (Grass). As a precaution to limit systematic observer bias, inspection of all data was delayed to after completion of all experiments.

A Maxitron X-ray unit, operated at 250 kvp, 25 ma. (HVL of 2.3 mm. Cu), was used for a 1,000 r exposure delivered in 9 minutes or 60 minutes. The dose rate for animals in the high intensity exposure group was nominally 1.9 r/sec. (1.5 - 2.5 r/sec., depending upon the animal's position in the chamber) and for the low intensity exposure group the rate was 0.25 r/sec. (0.22 - 0.28 r/sec.). Control animals were placed behind lead shields in the X-ray room.

To obtain adequate samples, 7 or 8 animals in each of 12 identical experimental runs were used. No differences among runs were apparent and data from all runs were combined in the analysis. From

5 minutes before through 15 minutes after the start of exposure five sampling intervals per minute were scheduled, each of 12 seconds duration. Two to three samples per minute were obtained from each animal on each variable during this period. This report presents the data obtained during the first minute of exposure from animals rated as asleep and completely inactive over the three intervals just prior to exposure.

Panel A of Fig. 2 shows the relative incidence of behavioral arousal (top) and of mean heart rate (bottom) during the first minute of exposure. Both exposed groups showed evidence of behavioral arousal within the first 12 seconds ($P < 0.02; \chi^2$). The high intensity exposure group subsequently exhibited a higher incidence of arousal ($P < 0.001; \chi^2$). Both groups were approaching the control group level of activity by the end of the first minute. Analysis of covariance was used on the heart rate data with the pre-exposure value serving as the concomitant variable in the analysis at each test point (7). The intra-class correlations were homogeneous among groups, high, and positive (+ .625 - + .928). The high intensity exposure group exhibited a peak in heart rate at about 30 seconds ($P < 0.005$; F) which corresponded in time to its peak incidence in behavioral arousal. These are not responses to a total dose since the low intensity exposure group, regardless of cumulative exposure time or dose, failed to exhibit any further responses beyond the behavioral response shown

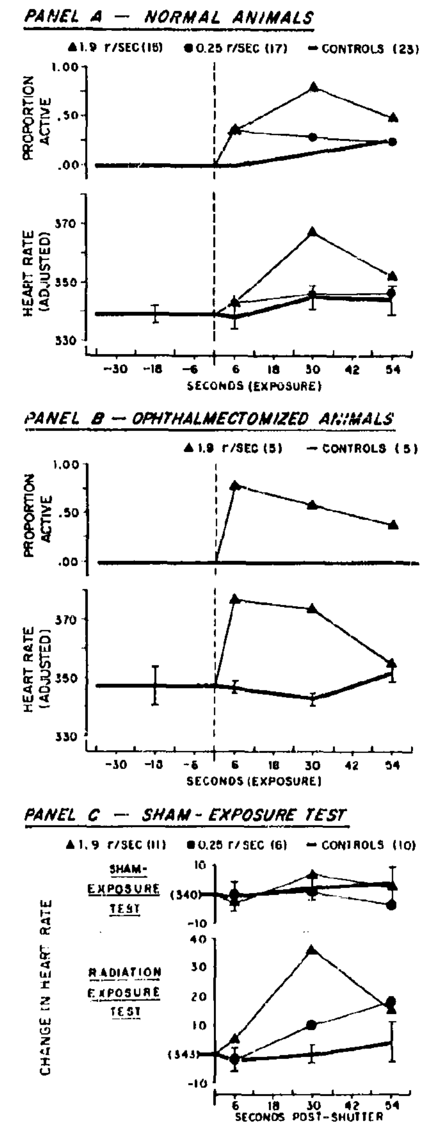

Fig. 2 The incidence of activity and mean heart rates in normal (Panel A) and ophthalmectomized (Panel B) animals. Heart rate means adjusted by analysis of covariance. Panel C shows mean changes in heart rates of normal rats that were asleep before both the sham-exposure (top) and radiation-exposure (bottom) tests. Standard error limits are indicated for control group heart rate means.

in the first measurement interval. It may be concluded that the threshold intensity of radiation exposure required to elicit diffuse neural activation, as indicated by the joint occurrence of the behavioral and heart rate responses, is between 0.25 and 1.9 r/second. A threshold intensity for activation limited to behavioral arousal, shown in the first interval of 12 seconds, is probably less than 0.25 r/second.

Presumably, a visual sensation of sufficient intensity to arouse an animal sleeping with eyes closed, and, therefore, partially dark-adapted, could be produced by X rays delivered at the intensities employed (8). To test this possibility, additional experimental runs were made using animals that had been subjected to complete, bilateral ophthalmectomy at one month prior to the exposure test. Panel B of Fig. 2 shows the results of this test. The arousal response appeared within the first measurement interval of 12 seconds. Hence, the arousal response cannot be attributed to direct retinal stimulation with ionizing radiation.

A procedural study was made to test for the presence of an arousing stimulus other than radiation, including possible residual noise from the sound-shielded shutter. A sham-exposure test was made in each experimental run at least 30 minutes before the radiation-exposure test. The results of these tests indicated that the arousal response cannot be ascribed to stimulation coincident with radiation. This can be shown most readily with the heart rate data obtained from normal rats that were asleep and inactive before both sham-exposure and radiation-exposure tests (Panel C of Fig. 2).

It is evident that ionizing radiation acts in a manner analogous to a stimulus in that it evokes a reflex-like arousal response in this behavioral preparation. The reaction is initiated in the presence of heightened sensory thresholds normally associated with sleep (10). It may be inferred from the behavior and heart rate data that the degree of neural activation underlying the response is related to the intensity of radiation. The arousal response is not dependent upon direct visual stimulation by X rays. The arousal reactions which arise after or continue beyond the first few seconds very likely involve reflex activation of the adrenal medulla (4,5).

Recent studies with mammals have shown that within the first minute of moderate intensity exposure gastric retention occurs (11), oxygen consumption increases (12), and EEG activity is altered (13). Although these responses might be related to the arousal response, arising as a consequence of central activation, they might also be primary responses to nervous stimulation with radiation. Reflex-like reactions to ionizing radiations have been described for invertebrates; the most sensitive reaction was found to be tentacle retraction in the snail (14). The arousal response in the rat would appear to be of comparable sensitivity.

The nervous mechanisms which are affected by radiation exposure in the production of behavioral arousal and central activation are obscure. Aside from photoreceptors, no sensory receptors have been demonstrated to be directly sensitive to radiation stimulation. Although the visual system is not essential for the reaction, it cannot be ruled out that stimulation through other receptor systems may initiate the central activation. Direct ganglionic sensitivity to ionizing radiation is also possible. This was proposed years ago by Toyama (15). More recently, Hug (14) has suggested that ionizing radiation may act like visible light in activating certain photosensitive processes in ganglionic structures. It may be that penetrating ionizing radiation is but one of a number of electromagnetic forms of energy to which nervous tissue is directly sensitive and one which would be particularly efficient for stimulating large masses of nervous tissue since the energy transfer would occur relatively uniformly with minimum spatial or temporal loss.

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